REMARKS

A. The Status of the Claims and the Amendments

By the present amendment, claims 105-108 and 112 have been amended to claim the invention with greater specificity, particularity, and accuracy. No new matter have been introduced in the amendments to the pending claims or with the new claims. For example, a limitation

> "wherein the path of administering of the protein-halide composition to the cell is selected from a group consisting of the administering through a cell membrane, cell wall, and nuclear membrane, or any combination thereof"

has been added to claim 105. This limitation is disclosed in the original specification (see, page 14, lines 16-18. Accordingly, entry of the amendment is respectfully requested.

Upon entry of this amendment, claims 105-116 will be pending, of which claims 105-110 are currently under consideration, and claims 110-116 are currently withdrawn.

B. The Restriction and Withdrawal of Claims 111-116

Claims 110-116 have been withdrawn from consideration as including "a new element," i.e., the application of ultrasound (see, Office Action, page 3, lines 2-3). The Applicants respectfully submit that such a withdrawal is improper because it is tantamount to making a restriction requirement without giving the Applicants a chance to make an election. In other words, the Examiner has declared that claims 110-116 are directed to a non-elected invention and *sua sponte* has withdrawn these claims from consideration. The Applicants respectfully believe that such an action is improper and strongly disagree with it.

Indeed, it is well established that the Examiner should notify the Applicants that the election is required (MPEP § 809.02 (a)), indicate how application is to be restricted (MPEP § 814) and to provide the reasons for the restriction, a statement of conclusion being inadequate (MPEP § 816). The Applicants must be given not less than 30 days make their own election or to traverse the requirement (MPEP § 809.02 (a)).

The above requirements have not been met. The Examiner has not previously made a restriction requirement as to the methods of protein delivery to the cell that he intended to search, and the Applicants have not been given an opportunity to traverse such a requirement, or, alternatively, to make their own election.

The Examiner's explanation is that a "new element" was introduced with claims 111-116. This is not a good enough reason to justify the withdrawal of these claims. The Examiner's further rationale is that all the new claims have been amended "beyond the originally filed subject matter" and to examine them now would require "an entirely new search" (see, page 2, lines 12-13 of the Office Action).

However, the Examiner, prior to withdrawing the claims, never explained why an extra search is needed now, because there is nothing in the pending Office Action specifying what kind of search he (or his predecessor) has already conducted.

It is the Applicants' understanding that a method of delivery recited in the original claim 1 would always require that certain steps be searched. The term "administering" recited in the original claim 1 is a generic term encompassing many specific methods of delivery, and if the Examiner, or his predecessor, wanted to restrict the search to any specific method of the administering, he should have stated so in the Restriction Requirement, and should have given the Applicants an opportunity to make an election. Instead, the Restriction Requirement mailed May 19, 2006, provided an eleven way restriction and a twenty-one way election of species requirements, but never asked the Applicants to select any specific method of delivery.

To summarize, in the Applicants' view, if the Examiner were correct, then any limitation as to a specific method of delivery added to the original claim 1 would introduce a new step to be searched, and thus will trigger the withdrawal of such an amended claim. Such an outcome is clearly absurd, because it would prevent the Applicants from amending the original claims, and there is nothing in patent laws or rules that would permit this. In view of the foregoing, reconsideration, withdrawal of the election of species requirement, and reinstatement of claims 111-116 are respectfully requested.

B. Rejections Under 35 U.S.C. § 102(b)

The Examiner mentioned rejections under 35 U.S.C. § 102(b) (page 4, line 15 through page 5, line 13 of the Office Action) over the references previously cited against claim 1, i.e., the following references: Stanko, Harth, Cella, Grimm, Pader '418, Pader '362, Kraus, Spero, Higuchi, Jederstrom, Cook '126, Cook '923, Cook '209, Witkowski, Golub, Gwaltney, Gristina, Sarzaud, and Love.

The Examiner has not stated explicitly whether the new claims 105-110 are also rejected over these or other references, despite the specific requirement that if a rejection is issued, the language used in rejecting claims must be unequivocal. See, MPEP § 706.02 and MPEP § 707.07 (d). The language in the present Office Action is confusing, and the Applicants respectfully request clarification as to whether claims 105-110 stand or do not stand rejected under 35 U.S.C. § 102(b) over the above-mentioned references. For the purposes of this response, and in order to avoid filing a defective and non-responsive response, for the time being the Applicantss assume that the Examiner did mean to issue such a 35 U.S.C. § 102(b) rejection. If so, the rejection is respectfully traversed.

It is worth noting that the Examiner has made a sweeping statement that the art is saturated by references describing compositions of proteins with halides and their delivery (see, page 5, lines 8-12 of the Office Action). The Applicants do not believe that

it is proper for an Examiner to make such a generalization, and further respectfully observe that the Examiner's statement is conclusory and lacks specificity.

Indeed, the Applicants respectfully submit that the above-mentioned terse statement made by the Examiner is not sufficient. The rules require an Examiner to provide a reasoned statement, and when a rejection is traversed, the Examiner is required, if the rejection is repeated, to take note of the applicant's argument and to answer the substance of it. See, MPEP § 707.07(f). In this case, in a previous response the Applicant argued that none of the nineteen references can qualify as a 102(b) reference. However, the Examiner summarily rejected this argument and has failed to explain why the argument was not persuasive. The Applicants respectfully submit that such treatment is improper and contradicts the rules promulgated by the MPEP.

The Applicants' position is quite simple and straightforward. It is well established that a valid rejection of a claim for anticipation by a reference requires that the reference explicitly or inherently describe all of the elements, limitations, and relationships recited in the claim. None of the above-described references teaches all the elements and limitations recited in claim 105.

In particular, claim 105 recites a method of delivery of a composition which requires a step of "combining the protein to be delivered and an organic halide," the halide being one of those further recited in claim 105. None of the references describe nor even suggest making such a combination.

Indeed, with respect to the first cited reference, there is nothing in Stanko teaching or suggesting the delivery of any protein, as required by claim 105. Stanko only described the delivery of isoprotenorol, which is not a protein (see, Stanko in col. 1, lines 15-18).

As to such references as each of Harth, Cella, Grimm, Pader '418 and Pader '362, none of them teaches or fairly suggests using any organic halide but chloroform. None of

the halides recited in claim 105 is used in any of Harth, Cella, Grimm, Pader '418 and Pader '362. One reason that claim 105 does not read on any of this references, is that claim 105 does not used chloroform; in other words, each of Harth, Cella, Grimm, Pader '418 and Pader '362, on the one hand, and claim 105, on the other hand, disclose the use of different halides, with no overlap.

The next two cited references, Kraus and Spero, disclose the use of a combination of a Freon, ammonia, and chloroform (Kraus) or the use of freons in combination with chlorinated butanol and an active compound such as acetonide (Spero). Like Stanko discussed above, neither Kraus nor Spero describes or suggests the use of any protein.

With respect to the next reference, Higuchi discloses the use of some halogenated solvents for the delivery of proteins, but does not describe or suggests using any organic halide recited in claim 105. Tricloro- and trifluoroethanol are the halides that Higuchi discloses and are not among the halides recited in claim 105. Accordingly, one reason that claim 105 does not read on Higuchi is that Higuchi, on the one hand, and claim 105, on the other hand, disclose the use of different halides, with no overlap.

With respect to the next six references, they contain the teachings of the use of fluorinated hydrocarbons for the delivery of 7-(β-hydroxypropyl)theophylline (Jederstrom) or the use of methylene chloride, chlorofluorocarbons or chloroform for delivering steroids by inhalation (each of Cook '126, Cook '923, and Cook '209), or the use of fluorinated hydrocarbons for the nasal delivery (Witkowski or Golub), such as antiviral agents comprising 1-B-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (Witkowski) or calcium-channel blocking agents, e.g., gallopamil (Golub).

There is nothing in Jederstrom or any of the three Cook references, or in Witkowski, or in Golub teaching or suggesting the delivery of any protein, as required by claim 105. Neither theophylline nor any steroid taught by Cook nor any antiviral compound taught by Witkowski nor any calcium-channel blocking agent of Golub is a protein.

Similarly, the next reference, Gwaltney discloses the use of fluorinated hydrocarbons for the nasal delivery of various medications, such as antiviral agents and anti-inflammatory compounds. A large number of antiviral and anti-inflammatory agent agents is disclosed by Gwaltney but none of them includes a protein, as required by claim 105.

Next, Gristina teaches the use of fluorinated hydrocarbons for delivery of various biocompatible particles, such as opsonized zymosan, PMMA latex, and polystyrene. None of these particles is a protein and there is nothing in Gristina describing or suggesting the use of any proteins to be delivered.

Similarly, the last two reference disclose the use of fluorinated hydrocarbons for delivery of various medications by transdermal administration (Sarzuad), or the use of fluorinated hydrocarbons for the delivery of asthma medications by inhalation (Love). Examples of drugs to be delivered include trinitrine, oestradiols and nicotine (Sarzaud) or steroids such as beclomethasone dipropionate (Love). There is nothing in Sarzaud or in Love teaching or suggesting the delivery of any protein, as required by claim 105.

Accordingly, none of the references discusses above describes or suggests all the limitations of claim 105, i.e., making a composition comprising both specific halides and proteins, followed by delivering such a composition into the cell, as required by claim 105.

In view of the foregoing it is submitted that claim 105 is patentably distinguishable over all the cited references, and each of claims 106-110 is considered patentable for at least the same reason, by the virtue of their dependency on claim 105. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) are respectfully requested.

C. Rejections Under 35 U.S.C. § 103(a)

Claims 105-110 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harth, or Cella, or Grimm, or Pader '418, or Pader '362, or Higuchi, or a combination thereof, in view of Stanko, or Kraus, or Spero, or Jederstrom, or Cook '126, or Cook '923, or Cook '209, or Witkowski, or Golub, or Gwaltney, or Gristina, or Sarzaud, or Love, or a combination thereof (page 6, lines 3-7 of the Office Action). These rejections are respectfully traversed on the following grounds.

The standard that has to be satisfied in order to make a valid rejection based on a prima facie case of obviousness was described in a response to a previous Office Action. This standard has been modified recently by the recent Supreme Court decision in the KSR International v. Teleflex Inc., 550 U.S. __, 127 S.Ct. 1727, 82 USPQ 2d. 1385 (2007), and there is no longer a strict requirement to satisfy the old " teaching-suggestion-motivation" standard to show obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references. The Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness either under the old standard or according to the modified standard.

In essence, the Examiner has separated the references into two groups. The first group of references (Harth, Cella, Grimm, Pader '418, Pader '362, and Higuchi) allegedly teaches the delivery of certain proteins (e.g., enzymes) in combination with halides, but none of the halides described is used in the present invention. The second group of references (Stanko, Kraus, Spero, Jederstrom, Cook '126, Cook '923, Cook '209, Witkowski, Golub, Gwaltney, Gristina, Sarzaud, or Love) allegedly teaches the

delivery of certain compounds in combination with various halides, but none of the compounds that are delivered as described in these references is a protein. The Examiner proposes to modify each of these references to arrive to what is claimed in claims 105-110, or, alternatively, to combine the references from these two groups to make out the *prima facie* case of obviousness.

The Applicants respectfully disagree with the Examiner's approach. Indeed, in the first group of references each of Harth, Cella, Grimm, Pader '418, Pader '362, as correctly pointed out by the Examiner, is directed to toothpaste formulations that include an enzyme. There is noting in these references indicating a delivery of any enzyme into any cell. It is submitted that the disclosures of these references provide no motivation whatsoever to modify them in a way suggested by the Examiner. There is no knowledge in the dental arts that would even remotely suggest that simple mechanical teeth brushing can possibly lead to the cells absorbing an enzyme. A simple contact of the enzyme with epithelial cells is indeed disclosed, but such a contact is not nearly enough to achieve the delivery, and the Examiner must realize this, as it is very clear to those skilled in the art. Indeed, the references explicitly teach that the enzymes are in fact used for different purposes, such as to dissolve dental tartar (see, e.g., Harth in col. 1, lines 40-41).

As to the Higuchi reference, it is true that it teaches administering of insulin, and perhaps some other proteins that are encompassed by antigens or vaccines. Certain fluorinated compounds are used in the delivery process. However, the invention described by Higuchi is so different from that claimed in the instant claim 105, that there are no reasonable grounds to believe that there could conceivably be any motivation to modify Higuchi in a way suggested by the Examiner.

First, the instant claim 105, as amended, requires that the entire protein-halide composition be delivered into a cell. In Higuchi, the fluorinated hydrocarbons are various freons (i.e., tricholofluoromethane or dicholodifluoromethane) and are used as propellants only, and clearly evaporate prior to any possible entry into any cell. Please,

also note that by the present amendment has been deleted from the Markush group recited in claim 105.

Second, as to "promoters" described by Higuchi (trichloroethanol, trifluoroethanol), the instant claims do not recite such compounds. To modify the instant claims over Higuchi means to use such promoters so that the promoter-protein combination would penetrate a cell. There is absolutely no such motivation in Higuchi. While it is clear that Higuchi uses halogenated promoters to improve the intake of a protein, there is no indication that the result of such facilitating of delivery will be the intracellular delivery of a protein-promoter combination. Nor is there any indication that any delivery will be through a cell membrane, cell wall, and nuclear membrane, as claim 105 now requires.

It is submitted that in a topical application described by Higuchi, it is much more likely that the protein alone, with no accompanying halide, will instead enter a body via the blood stream, or perhaps will be absorbed by dead skin cells that are always present on the surface. The Examiner did not show that what is taught by Iguchi is indicative of any likelihood of intracellular penetration. Accordingly, it is the Applicants' position that Iguchi, alone or in combination with any other reference cannot be used to establish a *prima facie* case of obviousness, as it fails to satisfy the KSR test described above.

Turing now to the second group of references identified by the Examiner (i.e., Stanko, Kraus, Spero, etc.) one can see that none of them describes delivery of any protein. The Examiner proposes to modify these references to extend the delivery methods to proteins. The Applicants respectfully disagree because there is no motivation to do so, and in any case, even if these references are modified in such a fashion, they would still fail to teach or suggest all of the limitations of claim 105.

For example, Stanko teaches delivery of a low molecular weight compound isoproteronol in combination with an alcohol and fluorinated hydrocarbons to a patient's bronchi or lungs. The fact that this compound touches the epithelial cells is not enough

to establish motivation, because there is no indication that the same or similar compositions that are appropriate to deliver isoproteronol will be also appropriate for delivering much heavier (i.e., having substantially greater molecular weight) proteins.

The same applies to the teachings of Kraus, Spero, Jederstrom, and Sarzaud that disclose the delivery of a low molecular weight freon 12 (Kraus), chlorobutanol (Spero), theophylline (Jederstrom) or trinitrine, oestradiols or nicotine (Sarzaud) in combination with halides. The fact that freon can be delivered that way provides no motivation to deliver a protein in a similar fashion, due to the great difference between the physical and chemical properties between freon, chlorobutanol, theophylline, trinitrine, oestradiols or nicotine on the one hand, and a protein, on the other hand. Each of the former compounds, freon, chlorobutanol, or theophylline, is different from the latter in every imaginable respect, including molecular weight, viscosity, volatility, solubility and so forth. There is nothing in these references or anywhere else which would suggest that the same delivery approach should apply for both kinds of compounds.

The same lack of motivation is clear when one reviews the teachings of Cook, Love, Witkowski, and Golub, that disclose the delivery of steroids (all three Cook references), corticosteroid beclomethasone dipropionate (Love), anti-viral medicine (Witkowski), or gallopamil or other calcium-channel blockers (Golub) in combination with halides. There is nothing in common between any of these compounds or any proteins, including chemical structure, reactivity, molecular weight, viscosity, volatility, solubility, etc. There is nothing in these references or anywhere else which would suggest the same delivery approach for both.

The same applies to the teachings of Gwalteny that disclose the delivery of various anti-viral or anti-inflammatory agents in combination with halides. Some examples of anti-viral agents that can be delivered include benzoimidazoles, 1'-methyl spiro(adamantane-2,3-pyrrolidine)maleate, isatin thiosemicarbazone, fusidic acid, etc. Some examples of anti-inflammatory agents that can be delivered include ipratropium,

atropine methonitrate, exogenous opioid agonists, alpha adrenergic agonists, chlorpheniramine, prostaglandin blockers and antagonists, leukotriene blockers and antagonists and so on. All the compounds delivered according to the method described by Gwaltey are completely different from proteins, chemically, physically, and in every other respect. There must be a strong motivation if the delivery approach adopted by Gwaltney is extended to delivery of proteins. There is no such motivation in these Gwalteny or anywhere else.

Finally, Gristina teaches delivery of phagocytosable particles, such as of biodegradable particles, opsonized zymosan, PMMA latex, polystyrene, heat killed-BCG, and heat killed Staphylococcus epidermis, in combination with fluorinated hydrocarbons. Obviously, there is nothing common between these products ranging from synthetic polymer (PMMA) to bio materials, and proteins. The same rationale applies here as discussed above. Short of having a strong motivation to do so, one skilled in the art would not use the same delivery methods for these phagocytosable particles and for proteins. Gristina is not a reference providing such a motivation.

he Applicants would like to reiterate that even if there were motivation to deliver protein by the above described method, the *prima facie* case of obviousness still could not be made out based on these reference because even if these references are modified as proposed by the Examiner, they would still fail to teach or suggest all of the limitations of claim 105.

More specifically, the references, as modified or combined do not teach or fairly suggest that the delivery of a protein is achieved "through a cell membrane, cell wall, and nuclear membrane," and that "the intracellular delivery of the protein" is accomplished as a result. Such a result cannot be inferred from any reference provided by the Examiner, because at the most they describe not more than a minimal surface contact of a compound to be delivered with epithelial cells. Such contact is insufficient to ensure the intracellular delivery through a cell membrane, cell wall, or nuclear membrane.

In view of the foregoing, it is submitted that claim 105 is patentably distinguishable over each of Harth, Cella, Grimm, Pader '418, Pader '362, Higuchi, Stanko, Kraus, Spero, Jederstrom, Cook '126, Cook '923, Cook '209, Witkowski, Golub, Gwaltney, Gristina, Sarzaud, and Love, or any combination thereof. Each of claims 106-110 depends claim 105 and is patentably allowable for at least the same reason. Accordingly, reconsideration and withdrawal of the rejection of claims 105-110 under 35 U.S.C. §103(a) are, therefore, respectfully requested.

D. Double Patenting Rejection

Claims 105-110 stand rejected under the non-statutory, judicially created doctrine of obviousness-type double patenting over claims 1-4 of U.S. Patent No. 6,638,767 (page 15, lines 6-8 of the Office Action).

While the Applicants respectfully traverse this rejection, it is believed that this issue has become moot in view of the terminal disclaimer which accompanies this response. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $65.00 as payment for the Statutory Disclaimer fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any fees that may be required by this paper, or credit any overpayment to Deposit Account 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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